REMARKS

The 28 April 2010 Official Action and the references cited therein have been carefully reviewed. In view of the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

Claims 1 – 30 and 38 – 45 were pending in the application; claims 1, 2, 7, 10, 13, 14, 39 – 41 and 43 – 45 are currently under consideration; claims 3 – 6, 8, 9, 11, 12, 15 – 30, 38, and 42 remain withdrawn from consideration.

Turning to the substantive aspects of the 28 April 2010 Official Action, the Examiner alleges that the Applicants have not complied with one or more of the conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §120, because the disclosure of the prior-filed U.S. Application No. 60/478,623, allegedly fails to provide adequate support or enablement for a lentivirus or engineered lentivirus that is infectious and replication-deficient. The Examiner thus concludes that the priority date of the claims presently under consideration is 14 June 2004, *i.e.*, the filing date of PCT/GB2004/02512.

The prior rejection (Official Action mailed 2 October 2009) of claims 1, 2, 7, 10, 13, 14, 39 – 41 and 43 – 45 under 35 U.S.C. §103(a) as allegedly unpatentable over Rovinski *et al.* and Esslinger *et al.*, has apparently been withdrawn. However, the Examiner now rejects claims 1, 2, 7, 10, 13, 14, 39 – 41 and 43 – 45 under 35 U.S.C. §103(a) as allegedly unpatentable over Casimiro *et al.*, 2003, J. Virol., 77:6305-6313 ("Casimiro"), Hill *et al.*, US 2003-0138454 A1 ("Hill") and Lewis *et al.*, 2001, J. Virol., 75:9339-9344 ("Lewis").

The foregoing constitutes the entirety of the conclusions and rejections raised in the 28 April 2010, Official Action. Each conclusion and rejection is traversed for the reasons set forth below. Applicants respectfully submit that the claims as instantly presented are patentable, and therefore, are in condition for allowance.

CLAIMS 1, 2, 7, 10, 13, 14, 39 – 41 and 43 – 45 ARE FULLY SUPPORTED, IN THE MANNER REQUIRED BY 35 U.S.C. §112, FIRST PARAGRAPH, BY THE DISCLOSURE OF PRIORITY DOCUMENT U.S. APPLICATION NO. 60/478,623

The Examiner has alleged that the claims currently under consideration are not entitled to the priority date of 13 June 2003 (the filing date of U.S. Provisional Application No. 60/478,623), and are only entitled to a priority date of 14 June 2004 (the filing date of

international application PCT/GB2004/02512), because the 60/478,623 allegedly does not provide any support for a lentivirus or engineered lentivirus that is infectious and replication-deficient. Applicants respectfully disagree.

While the conditions for entitlement to a priority claim include that the invention be disclosed in the earlier application in the manner provided by the first paragraph of 35 U.S.C. §112, there is no *in haec verba* requirement. Claim limitations can be properly supported in the specification through express, implicit, or inherent disclosure. MPEP §2163. With respect to the Written Description requirement, "[t]he fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." MPEP §2163 (I) (B) citing *Vas-Cath, Inc. v. Mahurkar* 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). With respect to the Enablement requirement, the earlier application provides an enabling disclosure if it would "permit one of ordinary skill in the art to make and use the claimed invention in the later filed . . . application without undue experimentation." MPEP §201.11 (I)(A).

Applicants submit that the disclosure of the 60/478,623 priority document fully supports the claimed methods for stimulating or boosting an immune response which use "infectious, replication-deficient lentivirus" (independent claim 1) or "infectious, replication-deficient lentivirus particles" (independent claim 13).

Evidence providing support for a lentivirus or lentivirus particle that is "infectious" is apparent throughout the disclosure of the 60/478,623 application. For example, at page 4, lines 13 – 14, the disclosure indicates that lentivirus contemplated for use in the methods of the invention is used to "directly infect antigen presenting cells," and at page 14, lines 5 – 9, the disclosure provides examples of low dosages of lentiviral particles contemplated for "[d]irect infection of an individual to activate an immune response." Moreover, the disclosure of 60/478,623 describes, at page 19, lines 2 – 24, the "infection" of .45 cells and human and mouse dendritic cells (DCs) using lentiviruses of the invention. It would thus be apparent to one of skill in the art, reading the disclosure of 60/478,623, that "infectious" lentivirus or lentivirus particles are contemplated for use in the methods of the invention.

Evidence providing support for a lentivirus or lentivirus particle that is "replication-deficient" is also apparent throughout the disclosure of 60/478,623. At page 16, lines 6 – 13

of the disclosure, it is stated that "[t]he preferred lentiviral vectors comprise modified lentivirus wherein the viral genes are deleted or modified so as to be inactive." Moreover, the exemplified embodiments in the disclosure of 60/478,623 utilize replication-deficient lentivirus. This replication-deficient characteristic would have been clearly understood by one of skill in the art reading the disclosure of 60/478,623. As described at page 18, lines 11 – 16, lentivirus particles were generated using pCMVR8.91 (Zufferey *et al.*, 1997, Nat. Biotechnol., 15:871 ("Zufferey")), in accordance with a previously described protocol (Neil *et al.*, 2001, J. Virol., 75:5448 ("Neil")). A review of Zufferey reveals that pCMVR8.91 (referred to as "pCMVΔR8.91") is a packaging plasmid for the production of HIV-1 viral particles lacking the virulence genes *env*, *vif*, *vpr*, *vpu* and *nef* (see Tables 1 and 2 of Zufferey). The lack of these genes renders the HIV-1 viral particles produced from pCMVR8.91 "multiply attenuated" (see Title, Abstract, and first paragraph of Discussion at page 873 of Zufferey). The authors note that "[t]he combined removal of [these] five genes eliminates the possibility that pathogenic HIV-1 recombinant might arise" because their respective encoded viral proteins are "proven or are strongly suspected to represent crucial virulence factors" (see second full paragraph at page 874, column 1). Additionally, it is clear that the authors considered the HIV-1 viral particles that they produced to be "replication-deficient" because they state that their "[v]ector stocks were tested for the absence of replication-competent HIV-derived virus" (see second paragraph in the Experimental Protocol at page 874 of Zufferey).

Finally, a review of Lewis (one of the references presently cited by the Examiner in support of the alleged obviousness rejection) reveals that Lewis also used the packaging vector pCMVΔR8.91 to generate viral particles, and Lewis refers to those viral particles as "replication-deficient" lentiviral vectors (see first two full paragraphs in column 1, and first full paragraph in column 2 at page 9340 of Lewis). This further confirms that the disclosure of 60/478,623 provides support for a "replication-deficient" lentivirus or lentivirus particle.

Clearly, it would be apparent to one of skill in the art of lentiviral replication, reading the disclosure of 60/478,623, that the priority document fully describes and enables use of lentivirus or lentivirus particles that are "replication-deficient.

Further, with reference to the above discussion regarding evidence providing support for a lentivirus or lentivirus particle that is "infectious", the HIV-1 viral particles produced by

Zufferey from pCMVR8.91 are also "infectious." Zufferey's multiply attenuated viral particles were able to transduce cells in culture and to deliver genes *in vivo* (see Abstract), and remained "fully infectious" (see Tables 1 and 2 and the first full paragraph of page 874, column 1 of Zufferey). Additional evidence is provided by Neil, where viral particles made with the same CMVR8.91 packaging plasmid (referred to as "pCMVΔR8.9") are also capable of infecting cells (see Figures 1A and 2), and by Lewis, where "infectious titers" of vector particles were generated using the pCMVΔR8.9 packaging plasmid (see first full paragraph in column 2 at page 9340, and Table 1 at page 9341 of Lewis).

In view of all of this evidence, one of skill in the art, reading the disclosure of 60/478,623 would have concluded that the Applicants were in possession of methods for stimulating or boosting an immune response which use "infectious, replication-deficient lentivirus." With respect to the enablement of such methods, Applicants submit that the disclosure of 60/478,623 is replete with instruction as to how to make and use "infectious, replication-deficient lentivirus" in the methods for stimulating or boosting an immune response.

Applicants respectfully request that the Examiner reconsider his position with respect to the priority claim for the claims presently under consideration and officially recognize that priority date to be the date of filing of U.S. Application No. 60/478,623, *i.e.*, 13 June 2003.

CLAIMS 1, 2, 7, 10, 13, 14, 39 – 41 and 43 – 45 ARE PATENTABLE OVER CASIMIRO, HILL AND LEWIS

At page 3 of the Official Action, the Examiner has rejected claims 1, 2, 7, 10, 13, 14, 39 – 41 and 43 – 45 as allegedly being unpatentable over Casimiro, Hill and Lewis.

It is the Examiner's position that Casimiro teaches a prime-boost immunization protocol for inducing an immune response to HIV-1 viral internal structural protein Gag. In order to induce the immune response, Casimiro describes administering to macaques a priming DNA encoding the *gag* gene, followed by administering infectious, replication deficient Adenovirus serotype 5 also encoding the *gag* gene. The reference is also relied on for teaching that an increase in peripheral blood mononuclear cells is observed after the boost administration relative to the priming dosage and that an increase in CD8+ T cells producing IFNγ is observed. The Examiner admits that Casimiro does not teach the use of an infectious,

replication deficient lentivirus engineered to encode an exogenous nucleic acid sequence of an antigen.

Further, it is the Examiner's position that Hill teaches a prime-boost immunization protocol using DNA or proteins of an antigen of interest (including HIV envelope antigens) for priming, followed by a replication deficient poxvirus that encodes the antigen of interest. The Examiner admits that Hill, like Casimiro, does not teach the use of an infectious, replication deficient lentivirus engineered to encode an exogenous nucleic acid sequence of an antigen.

The Examiner relies on Lewis for teaching the development of an infectious, replication deficient lentivirus vector to address the deficiencies of the Casimiro and Hill references. Surprisingly, in view of the teachings of these references, the Examiner concludes that it would have been obvious for one of ordinary skill in the art to modify the methods of Casimiro and Hill in order to use lentivirus that is infectious but cannot replicate in a heterologous prime-boost method, given the teaching of Lewis that recombinant replication deficient, infectious lentiviruses can be generated and can express exogenous proteins, such as green fluorescent protein (GFP).

The objective analysis for determining obviousness under 35 U.S.C. §103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). Obviousness is a question of law based upon factual inquiries into 1) the scope and content of the prior art, 2) the differences between the claimed invention and the prior art, and 3) the level of ordinary skill in the pertinent art. It is the Examiner's burden to establish the Graham factual findings and to articulate reason(s) why a claimed invention would have been obvious. An obviousness rejection "cannot be sustained by mere conclusory statements; . . . there must be some articulated reasoning with some traditional under pinning to support the legal conclusion of obviousness." *In re Kahn*, 78 U.S.P.Q.2d 1329, 1336 (Fed. Cir. 2006). Moreover, the mere fact that references can be combined or modified does not render the resulting combination obvious unless the prior art also suggests the desirability of the combination. MPEP § 2143.01, citing *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Considering the foregoing, Applicants respectfully traverse the rejection for the following reasons.

Casimiro presents the evaluation of several DNA vaccine formulations, a modified vaccinia virus Ankara vector, and a replication-defective adenovirus serotype 5 (Ad5) vector,

each expressing the same codon-optimized HIV-1 *gag* gene, for immunogenicity in rhesus macaques (see Abstract). Their results showed that the adenovirus type-5-mediated gene transfer provided an extremely potent means of inducing anti-HIV-1 T cell responses, in particular CTL. By contrast, DNA vectors were notably less immunogenic, but were enhanced by formulation with adjuvants, and the MVA vector elicited mimimal cellular immune responses as a single modality (see Discussion at pages 6310 – 6311). Casimiro found that the Ad5-*gag* vector could be used effectively in a prime-boost regime (particularly as a boost following priming with an adjuvant-formulated DNA vaccine) to yield extremely potent anti-HIV-1 Gag T cell responses, that were not negatively influenced by pre-existing immunity to the viral vector itself (see Figure 6 and first full paragraph at page 6312, column 2). Casimiro concludes that the data suggest an "immunization strategy for humans . . . [using] the adenovirus vector and in which existing adenovirus immunity may be overcome by combined immunization with adjuvanted DNA and adenovirus vector boosting" (see Abstract).

Hill relates to methods of inducing CD4+ and/or CD8+ T cell responses based on the discovery that non-replicating and replication-impaired strains of poxvirus provide vectors which give an extremely good boosting effect to a primed CTL response (see paragraph 11). Hill demonstrates that the use of heterologous prime-boost regimes with replication-impaired poxviruses generated very high levels of CD8+ T cells and induced unprecedented complete protection against *P. berghei* sporozoite challenge in mice (rodent models of human malaria infection) (see paragraphs 287 – 289), was highly immunogenic in higher primates and induced partial protection against *P. falciparum* challenge (see Example 13), and induced protective immune responses in mouse models of viral infection (influenza A) and cancer (P815 tumor model) (see Example 4).

In describing the success achieved in humans in enhancing T cell immunogenicity against malaria using plasmid DNA vaccines boosted by recombinant modified vaccinia virus Ankara (MVA), Hill states that "[t]he results indicate that, as in animals, DNA priming followed by MVA-boosting vaccination produces large cellular responses, which far surpass the responses seen after either vaccine alone" (see paragraph 514). Furthermore, Hill praises the desirable characteristics of recombinant MVA as particularly effective for boosting T cell responses, adequate at single doses, and having an excellent safety profile in monkeys and

humans (see paragraph 518). Based on these characteristics and the success in achieving improved immune responses against a malaria parasite, Hill concludes that a vaccination strategy using a non-replicating or replication-impaired poxvirus in the boosting step "could be the basis for effective vaccines for malaria, HIV, Hepatitis B virus, tuberculosis and tumours." Additionally, Hill states that "[t]he pox virus vector described herein may be particularly useful for boosting CD4 T cell responses in HIV-positive individuals" (see paragraph 174).

Lewis developed a replication-deficient, HIV-1-based lentiviral vector, pseudotyped with the envelope glycoprotein for avian leukosis-sarcoma virus (ALSV) subgroup A, to be used for the initiation of tumorigenesis in resting, TVA (the receptor for subgroup A ALSV)-positive cells in transgenic mice. Notably, the vector developed by Lewis retains the specificity of ALSV-based vectors, infecting only those mammalian cells engineered to express TVA, but unlike previous vectors, it can infect both primary cells **and** non-dividing and terminally differentiated cells (see Abstract).

The present invention relates to a heterologous prime-boost immunization protocol where an infectious, replication-deficient lentivirus vector is used as a carrier of nucleic acid encoding the antigen of interest in either the priming step or the boosting step (claim 1 allows for either, but not both; claim 13 requires the replication-deficient lentivirus be used as the boost).

The Examiner states, at page 5 of the Official Action, that the motivation to use the replication deficient, infectious lentivirus of Lewis in place of the adenovirus type 5 vector of Casimiro or the poxvirus of Hill is based on the suggestion by both Casimiro and Hill that improved immune response to HIV proteins could be achieved via heterologous prime-boost immunization protocols using DNA encoding the protein and a replication deficient virus.

Applicants submit that Applicants' claimed invention would not have been obvious to one of ordinary skill in the art. There simply would have been no motivation to combine the references as suggested by the Examiner, and the Examiner has failed to show why one of ordinary skill in the art would have been motivated to modify the teachings of either Hill or Casimiro by using the replication deficient, infectious lentivirus of Lewis.

It is apparent, from a review of Hill that the crucial feature of the preferred embodiments of their method is the use of a non-replicating or replication-impaired poxvirus

to deliver the antigen of interest. Indeed, Hill states that "[t]he critical step in this immunization regimen is the use of non-replicating or replication-impaired recombinant poxviruses to boost a pre-existing CTL response" (see paragraph 357). It is not logical to conclude that the skilled artisan would be motivated to modify the crucial feature of Hill (*i.e.*, a non-replicating or replication-impaired poxvirus must be used for the boost), since the procedure disclosed in the reference worked as intended. The Examiner suggests that such motivation might be founded in a desire to improve immune responses to HIV proteins. Yet Hill teaches that one should use their immunization regime, *i.e.*, using a non-replicating or replication-impaired poxvirus as the boost, to achieve such a goal ("Similarly the plasmid DNAs and MVA endoding HIV epitopes for human class I molecules could be used in either prophylactic or therapeutic immunisation against HIV infection." See paragraph 356).

Hill teaches that the use of non-replicating or replication-impaired poxvirus in the boosting step of heterologous prime-boost immunization regimes is effective for improved immune responses to such antigens as HIV antigens. Applicants submit that one of skill in the art, reading Hill, would conclude that non-replicating or replication-impaired poxvirus would be the appropriate choice for the boost vector in a heterologous prime-boost immunization protocol. Applicants submit that it would not be logical to use a lentiviral vector in view of the teachings of Hill. In view of the teachings of Hill, if one of skill in the art wanted to improve immune responses to HIV proteins, he or she would use a non-replicating or replication-impaired poxvirus, such as MVA, and would follow a protocol such as that employed by Hill in Example 5, where a DNA priming/MVA boosting regime yielded strong immunogenicity in macaques against CTL epitopes derived from HIV and SIV (see paragraphs 337 – 344).

Similar reasoning for a lack of motivation to combine applies to Casimiro, where there would be no motivation to use a different vector system (to change from an adenovirus type 5 vector to a lentivirus vector) where the results of the study indicated that replication-defective Ad5 vectors would be an excellent choice for a boosting vector in a heterologous boost-prime protocol for improving immune responses to an antigen of interest, in particular an HIV protein. One of skill in the art reading Casimiro would not consider it necessary or desirable to replace the Ad5 vector with any other type of viral vector, much less a lentiviral vector, when the system presented by Casimiro worked for its intended purpose. Moreover,

Casimiro showed that the common problem of existing immunity to adenovirus type 5 in humans is not a major issue with the use of the Ad5 vector, and may be overcome by combined immunization with adjuvanted DNA and adenovirus boosting (see Abstract and first full paragraph in column 2, page 6312). Indeed, based on the results of the study in Casimiro, human "[c]linical trials have been designed to assess tolerability and immunogenic potential in humans of adenovirus type 5 vectors expressing the HIV-1 Gag protein, either alone or in prime-boost regimens with adjuvanted DNA vectors" (see last paragraph at page 6312, column 2).

The aim of the study in Lewis was to expand TVA-directed gene delivery from only actively dividing cells to nondividing and terminally differentiated cells (see page 9339, col. 2 to page 9340, col. 1). The lentiviruses of Lewis were specially designed to target only cells expressing the TVA receptor protein, and Lewis only tested them for their ability to introduce genes into the somatic cells of TVA transgenic mice. The special design involved psuedotyping such that the lentiviral particles prepared possessed the envelope protein ALSV subgroup A (EnvA) to enable targeting only to cells expressing TVA on their surface. Lewis does not teach or suggest the suitability of their lentiviral particles for stimulating immune responses, much less methods of heterologous prime-boost immunization protocols or for boosting pre-existing immune responses. Thus, Applicants submit that one of ordinary skill in the art would not be motivated to use the lentiviruses of Lewis in combination with either Casimiro or Hill in heterologous prime-boost immunization protocols.

Applicants' claimed invention would not have been obvious to one of ordinary skill in the art. There simply would have been no motivation to combine the references as suggested by the Examiner. Moreover, Applicants urge that the Examiner has impermissibly used Applicants' disclosure in hindsight for the teaching that an infectious, replication-deficient lentivirus vector, such as described in Lewis, could be used in place of the adenovirus type 5 vector of Casimiro or the poxvirus of Hill with any reasonable expectation of success. Casimiro and Hill clearly teach away from using any other viral system beside adenovirus type 5 and poxvirus, respectively, and Lewis is silent with respect to stimulating, much less boosting, immune responses.

In view of all the foregoing, Applicants submit that the examiner has failed to establish a prima facie case of obviousness based on the combined disclosures in the cited

references and request that the rejection of claims 1, 2, 7, 10, 13, 14, 39 – 41 and 43 – 45 under 35 U.S.C. §103(a) be withdrawn.

Conclusion

It is respectfully requested that the amendments presented herewith be entered in this application. The present remarks are believed to clearly place the claims under consideration (claims 1, 2, 7, 10, 13, 14, 39 – 41 and 43 – 45) in condition for allowance. Therefore, it is respectfully urged that the rejections set forth in the 28 April 2010 Official Action be withdrawn and that this application be passed to issue.

If a fee is required or an overpayment is made, the Commissioner is authorized to charge or credit the deposit account of the undersigned, Account No. 04-1406.

Early and favorable action on the present application is earnestly solicited.

Respectfully submitted,

DANN DORFMAN HERRELL and SKILLMAN, P.C.
Attorneys for Applicants

Date: 24 September 2010

/Robin S. QUARTIN, Reg. No. 45,028/
Robin S. Quartin, J.D., Ph.D.

Registration No. 45,028
Telephone: 215-563-4100
Facsimile: 215-563-4044
E-mail: rquartin@ddhs.com